REMARKS

Justification for the amendments is as follows. The specification has been amended to delete references to certain web sites. The claims have been amended to clarify the invention. In particular, claim 1 has been amended to recite the term "comprising" and to recite "the complement" of cDNAs. Claims 1 and 3 have been amended to recite naturally occurring variants of SEQ ID NO:1 and SEQ ID NO:3, respectively having at least 90% sequence identity with SEQ ID NO:1 and SEQ ID NO:3, respectively. Support for the amendments to claims 1 and 3 are found in the specification, for example, at p. 11, lines 14-20 which describe naturally occurring allelic variants and splice variants of SEQ ID NOs:1 and 3. Applicants do not concede to the Patent Office position; Applicants are amending the claims solely to obtain expeditious allowance of the instant application. No new matter is added by any of these amendments, and entry of the amendments is requested.

35 U.S.C. § 112, First Paragraph, Rejection of Claims 1-4 and 6-8

The Examiner has maintained the rejection of claims 1-4 and 6-8 under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the previous Office Action. The Examiner stated that Applicants traversal is on the grounds that the specification discloses the cDNA and fragments and variants thereof may be used in hybridization, amplification, and screening technologies to identify and distinguish between SEQ ID NO:1-2 and related molecules. However, the Examiner stated, Applicants arguments are not persuasive because the invention of claims 1 (b) and 3 (c) are drawn to a cDNA encoding a protein variant having at least 80% identity to SEQ ID NO:1 and a cDNA or the complement thereof comprising a variant of SEQ ID NO:3 which is at least 80% identical to SEQ ID NO:3, and that this includes a whole universe of cDNA with 80% identity to SEQ ID NO:1 and/or 3. The Examiner stated that one skilled in the art would not know how to select for the claimed invention because there is no guidance as to what function the cDNA must possess in order to function as contemplated. The Examiner stated that the rejection may be overcome if the claim werre to recite an activity for the protein which the cDNA encodes or what function the cDNA possesses.

Applicants reiterate the arguments presented previously in response to the previous Office Action that such variants may be used to distinguish between SEQ ID NOs:1 and 2 and related molecules using amplification and hybridizations techniques well known in the art and described in the specification, regardless of the function of the encoded protein. However, in the interest of expediting prosecution and

the allowance of claims, Applicants have further limited such claimed variant sequences to "naturally occurring" variants having at least 90% sequence identity to SEQ ID NO:1 and/or 3. Naturally occurring variant sequences are both known in the art and described in the specification to be limited in scope. For example, splice variants are described in the specification at p. 11, lines 4-5 as having a high degree of homology by BLAST analysis, and allelic variants are likewise described as having "a high percent identity to the cDNAs and may differ by about three bases per hundred bases". Thus one skilled in the art would recognize such variants as very limited in scope and clearly not including a "whole universe" of cDNA as the Examiner alleges.

With respect to claimed variants of SEQ ID NO:1 and the Examiner requirement that such variants be recited in functional terms, Applicants submit that the requirements necessary to fulfill the written description requirement of 35 U.S.C. 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.* *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, to which the Examiner has made reference, and which provide that :

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics[42] which provide evidence that applicant was in possession of the claimed invention,[43] i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.[44] What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail.[45] If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.[46]

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

SEQ ID NO:1 is specifically disclosed in the application (see, for example, page 12, lines 13-14). Variants of SEQ ID NO:1 are described, for example, at page 11, lines 14-20. Incyte clones in which the nucleic acids encoding the human IP-1 were first identified and libraries from which those clones were isolated are described, for example, at page 11, lines 27-30 of the Specification. Chemical and structural features of human IP-1 are described, for example, on page 12, lines 14-27. Given SEQ ID NO:1, as well as the structural features identified within SEQ ID NO:1, one of ordinary skill in the art would recognize variants of SEQ ID NO:1 having at least 90% sequence identity to SEQ ID NO:1. Accordingly, the specification provides an adequate written description of the recited polypeptide sequences.

1. The present claims specifically define the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue (which are hence relevant to claims to proteins encoded by the DNA) commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

> 1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

> A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. §112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define polynucleotides in terms of chemical structure, rather than on functional characteristics. For example, the "variant language" of independent claim 1 recites chemical structure to define the claimed genus:

> 1. An isolated mammalian $cDNA_x$ or the complement thereof, comprising a sequence encoding a mammalian protein selected from:--- b) a naturally occurring variant having at least 90% amino acid sequence identity to the amino acid sequence of SEQ ID NO:1;---.

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1. In the present case, there is no reliance merely on a description of functional characteristics of the polynucleotides recited by the claims. In fact, there is no recitation of functional characteristics relative to the claimed variants of SEQ ID NO:1. Moreover, if such functional recitations were included, it would add to the structural characterization of the recited polynucleotides. The polynucleotides defined in the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims of this type. By failing to base its written description

inquiry "on whatever is now claimed," the Office Action failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*.

2. The present claims do not define a genus which is highly variable

Furthermore, the claims at issue do not describe a genus which could be characterized as highly variable. Available evidence illustrates that the claimed genus is of narrow scope.

In support of this assertion, the Examiner's attention is directed to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <40% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., pages 6073 and 6076.) Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner et al., page 6076.)

The present application is directed, *inter alia*, to intestinal proteins related to the amino acid sequence of SEQ ID NO:1. In accordance with Brenner et al, naturally occurring molecules may exist which could be characterized as IP-1 proteins and which have as little as 40% identity over at least 70 residues to SEQ ID NO:1. The "variant language" of the present claims recites, for example, polynucleotides encoding "a variant having at least 90% identity to the amino acid sequence of SEQ ID NO:1" (note that SEQ ID NO:1 has 475 amino acid residues). This variation is far less than that of all potential proteins related to SEQ ID NO:1, i.e., those proteins having as little as 40% identity over at least 70 residues to SEQ ID NO:1. Considering this and the fact that the specification recites numerous chemical and structural features of human IP-1 on page 12, lines 14-27, the genus of claimed variants is well defined and not highly variable.

2. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. §112. The '525 patent claimed the benefit of

priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written description inquiry in those case was based on the state of the art essentially at the "dark ages" of recombinant DNA technology.

The present application was filed on Decebmer 4, 2000. Much has happened in the development of recombinant DNA technology in the 20 or more years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances one of skill in the art would recognize that, given the sequence information of SEQ ID NO:1, and the additional extensive detail provided by the subject application, the present inventors were in possession of the claimed polynucleotide variants of SEQ ID NO:1 at the time of filing of this application.

3. Summary

The Office Action failed to base its written description inquiry "on whatever is now claimed." Consequently, the Action did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1 and relevant subsequences. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids and proteins. In addition, the genus of variant polynucleotides defined by the present claims is adequately described, as evidenced by Brenner et al and consideration of the claims of the '740 patent involved in *Lilly*. Furthermore, there have been remarkable advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Office Action.

For all of the above reasons, Applicants submit that they were in possession of the claimed invention, as amended, at the time the application was filed, and that the claimed invention is fully enabled by the specification. Applicants therefore request withdrawal of the rejection of claims 1-4 and 6-8 under 35 U.S.C. § 112, first paragraph.

Withdrawal of Claims Rejection under 35 U.S.C. § 102

The Examiner has withdrawn the rejection of claims 1-2 and 4-8 as being anticipated by Bool et al. (1993).

NEW CLAIM REJECTIONS

35 U.S.C. § 112, Second Paragraph, Rejection of Claims 1(c) and 6

The Examiner has rejected claims 1(c) and 6 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. The Examiner stated that claim 1(c) recites antigenic epitopes of SEQ ID NO:1, however that it is not clear whether the antigenic epitope comprises SEQ ID NO:1 or a fragment thereof. Claim 1 has been amended to recite ". Claim 1 (c), prior to amendment, recites "An isolated mammalian cDNA encoding---an antigenic epitope of SEQ ID NO:1". An "epitope" or "antigenic epitope" of a protein is both well known in the art as well as defined in the specification as a "portion" or "fragment" of a larger protein such as SEQ ID NO:1. See, for example, p. 9, line 29-30 and p. 10, lines 7-10 of the specification, and at p. 13, lines 13-15 of the specification which provides examples of useful antigenic epitopes of SEQ ID NO:1. Clearly, an antigenic epitope comprises a "fragment" or "portion" of SEQ ID NO:1. However, in the interests of further clarifying the claimed polynucleotides, claim 1 has been amended to recite "An isolated mammalian cDNA --- comprising a sequence encoding –- an antigenic epitope of SEQ ID NO:1".

B. The Examiner also stated, likewise, that claim 6 is indefinite as it is unclear if the probe comprises SEQ ID NO:1 or a portion thereof. With the amendments to claim 1 recited above, a probe of claim 6 may therefore comprise a polynucleotide encoding SEQ ID NO:1, a polynucleotide encoding the recited variant of SEQ ID NO:1, a polynucleotide encoding an antigenic epitope of SEQ ID NO:1, or the complement of said polynucleotide.

Applicants therefore submit that with these amendments, claims 1 and 6 are clear and definite and request withdrawal of the rejection of claims under 35 U.S.C. § 112, second paragraph.

Objection to the Disclosure

The Examiner has objected to the disclosure because it contains an embedded hyperlink and/or other form of browser-executable code (page 32) and that this is not permitted according to MPEP § 608.01.

Applicants submit that the MPEP states at § 608.01 that this policy is based on the principle that "USPTO policy does not permit the USPTO to link to any commercial sites since the USPTO exercises no control over the organization, views or accuracy of the information contained on those outside sites (underline added). Section 608.01 goes on to state that "where hyperlinks and/or other forms of browser-executable codes are a part of the applicant's invention and it is necessary to have them included in the patent application in order to comply with the requirements of 35 U.S.C. 112, first paragraph, and applicant does not intend to have these hyperlinks as active links, examiners should not object to these hyperlinks. The Office will disable these hyperlinks when preparing the text to be loaded onto the USPTO web database (underline added). Applicants point out that the cited website is a non-commercial, government web site which should not be subject to the requirements of MPEP § 608.01. However, this citation, as well as a second at page 33, line 26 have been deleted. Withdrawal of the objection is therefore requested.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding objections and rejections. Early notice to that effect is earnestly solicited. Applicants further request that upon allowance of claim 1 that claims 9 and 11-15 be rejoined and examined as methods of use the the compositions of matter of claim 1 that depend from and are of the same scope as claim 1 in accordance with *Ochiai and Brouwer*. See MPEP § 821.04 and the Commissioner's Notice in the Official Gazette of March 26, 1996.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact Applicants' Agent of Record, below.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

Respectfully submitted,
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Docket No.: PC-0028 US

Version with markings to show changes made

IN THE SPECIFICATION:

Paragraph beginning at line 14 of page 32 has been amended as follows:

The BLAST software suite, freely available sequence comparison algorithms (NCBI, Bethesda MD[; **http://www.ncbi.nlm.nih.gov/gorf/bl2.html**]), includes various sequence analysis programs including "blastn" that is used to align nucleic acid molecules and BLAST 2 that is used for direct pairwise comparison of either nucleic or amino acid molecules. BLAST programs are commonly used with gap and other parameters set to default settings, e.g.: Matrix: BLOSUM62; Reward for match: 1; Penalty for mismatch: -2; Open Gap: 5 and Extension Gap: 2 penalties; Gap x drop-off: 50; Expect: 10; Word Size: 11; and Filter: on. Identity is measured over the entire length of a sequence or some smaller portion thereof. Brenner et al. (1998; Proc Natl Acad Sci 95:6073-6078, incorporated herein by reference) analyzed the BLAST for its ability to identify structural homologs by sequence identity and found 30% identity is a reliable threshold for sequence alignments of at least 150 residues and 40%, for alignments of at least 70 residues.

Paragraph beginning at line 20 of page 33 has been amended as follows:

Following assembly, templates were subjected to BLAST, motif, and other functional analyses and categorized in protein hierarchies using methods described in USSN 08/812,290 and USSN 08/811,758, both filed March 6, 1997; in USSN 08/947,845, filed October 9, 1997; and in USSN 09/034,807, filed March 4, 1998. Then templates were analyzed by translating each template in all three forward reading frames and searching each translation against the PFAM database of hidden Markov model-based protein families and domains using the HMMER software package (Washington University School of Medicine, St. Louis MO[; **http://pfam.wustl.edu/**]). The cDNA was further analyzed using MACDNASIS PRO software (Hitachi Software Engineering), and LASERGENE software (DNASTAR) and queried against public databases such as the GenBank rodent, mammalian, vertebrate, prokaryote, and eukaryote databases, SwissProt, BLOCKS, PRINTS, PFAM, and Prosite.

IN THE CLAIMS:

Claims 1 and 3 have been amended as follows:

1. (Twice Amended) An isolated mammalian cDNA, or the complement thereof, comprising a sequence encoding a mammalian protein selected from:

a) an amino acid sequence of SEQ ID NO:1;

b) a naturally occurring variant having at least 90[80]% amino acid sequence identity to the amino acid sequence of SEQ ID NO:1; and

c) an antigenic epitope of SEQ ID NO:1.

3. (Thrice Amended) An isolated mammalian cDNA or the complement thereof comprising a sequence selected from:

a) a nucleic acid sequence of SEQ ID NO:3;

b) a fragment of SEQ ID NO:3 from about nucleotide 170 to about nucleotide 220, from about nucleotide 1015 to about nucleotide 1055, or from nucleotide 1500 to 1550 of SEQ ID NO:3; and

c) a naturally occurring variant of SEQ ID NO: 3 having at least 90[80]% sequence identity to the nucleic acid sequence of SEQ ID NO:3.